University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS
TEMPLATE WITH GUIDANCE

Version date: January 11,2023

Principal Investigator: Nikki Nollen

Study Title: The Impact of Menthol Flavoring on Switching in Adult Menthol Smokers

Co- Investigator(s): Lisa Sanderson Cox, Eleanor Leavens, Matthew Mayo

---

I. Purpose, Background and Rationale

A. Aims and Hypotheses

Nearly 12 of the 34 million adult smokers in the US smoke menthol cigarettes. When added to cigarettes, menthol increases addictive potential and dependence, and decreases the likelihood of cessation. These effects are particularly felt in the African American (AA) community where targeted marketing has resulted in ≈85% of AA versus ≈20% of White smokers using menthol cigarettes. The FDA's decision to advance the rulemaking process to ban menthol cigarettes is an important step toward closing the gap in tobacco-related disease and death disproportionately experienced by AA smokers. The agency's regulatory action stopped short of including menthol-flavored e-cigarettes (ECs) and debate continues about whether more comprehensive enforcement priorities inclusive of menthol flavored e-liquids should be enacted. While a ban on menthol flavored EC liquids may reduce youth and young adult initiation, it may also discourage adult menthol smokers to switch from tobacco cigarettes to EC. This could slow harm reduction and result in a negative public health impact that would be concentrated in racial/ethnic minority communities already disproportionately burdened by tobacco. FDA has identified the impact of EC flavoring on smoking patterns as a research priority area, and there is an **urgent need** for studies that examine tobacco regulatory actions with a specific focus on possible unintended consequences that may increase tobacco-related health disparities. *To date, a prospectively designed randomized clinical trial (RCT) has not been conducted; therefore, the efficacy of menthol-flavored versus tobacco-flavored EC to facilitate switching from combustible cigarettes to EC in adult menthol smokers is not known.* Our experienced, multi-disciplinary team is one of the only groups in the country exclusively focused on tobacco-related health disparities intervention research in the AA community. Our recently completed RCT provided menthol EC or tobacco EC to AA and Latinx adult smokers. Among menthol smokers, post-hoc analyses found equivalent rates of switching from tobacco cigarettes to EC, tobacco harm reduction, EC product use, and acceptability between those who used tobacco EC versus menthol EC, although the study was not prospectively designed for this purpose and is limited by a small sample size for these comparisons. These data are consistent with observational studies that have found that nicotine – not flavor – drive use in adult EC users and provide strong preliminary evidence to support restrictions on menthol flavored EC given potential benefit to youth and lack of evidence of harm to smokers. However, to empirically answer this question, a fully powered RCT is needed.

The *objective of this application* is to provide much needed data to the FDA to guide regulatory action on EC flavoring. Menthol smokers (n=800), stratified by race and gender, will be randomized 1:1 into a 12-week open label, non-inferiority trial comparing a 4th generation nicotine salt-based pod-system EC in menthol- versus tobacco-flavored e-liquid. Follow-up will continue through week 26. The **central hypothesis** is that tobacco EC are not inferior to menthol EC at facilitating a switch to EC in menthol cigarette smokers.

Our specific aims are:

1) **Compare the effectiveness of menthol versus tobacco EC at facilitating switching at week 12.** Hypothesis 1: Participants randomized to tobacco EC (versus menthol EC) will demonstrate non-inferior rates of complete and predominant switching to EC (primary outcome). Complete switching is defined as exclusive use of EC, confirmed with CO < 6 ppm, and predominant switching is defined as use of EC with > 50% reduction in CPD. Rates of complete and predominant switching will also be compared separately by group.

2) **Compare tobacco harm reduction of menthol versus tobacco EC at week 12.** Participants randomized to tobacco EC (versus menthol EC) will demonstrate comparable (i.e., no statistically significant differences) change in CO, respiratory symptoms, lung function, blood pressure, and tobacco-related quality of life from baseline to week 12.
3) **Compare the acceptability of menthol versus tobacco EC at week 12.** Hypothesis 3: Participants randomized to tobacco EC (versus menthol EC) will consume comparable amounts of study provided e-liquid (measured in grams) and demonstrate comparable reductions in cigarette-related withdrawal, craving, and dependence. Subjective effects of vaping will also be compared between groups.
4) **Examine the long-term effectiveness of menthol versus tobacco EC at week 26.** Switching patterns at week 26 will be compared to examine long-term maintenance of EC and smoking patterns under naturalistic conditions (EC only provided up to week 12). Hypothesis 4: There will be no statistically significant difference in rates of complete or predominant switching at week 26 between those randomized to menthol versus tobacco EC.

B. Background and Significance

Electronic cigarettes as a harm reduction strategy for adult cigarette smokers. Tobacco, but primarily cigarettes, remains the leading cause of preventable disease in the US, claiming 480,000 lives per year and affecting an additional 16 million smokers who suffer from smoking-related chronic diseases.[1] Eliminating tobacco use in adult cigarette smokers remains the primary end-game for reducing tobacco's public health burden,[2] but tobacco harm reduction has emerged as an important complement to these efforts.[3] Specifically, the availability of potentially less harmful products has led to increased focus on replacing all forms of combustible tobacco with noncombustible nicotine products that deliver nicotine but fewer tobacco toxicants to adults who cannot or are not ready to quit cigarettes. Central to harm reduction is the fact that nicotine contributes relatively little harm compared to the deleterious effects of combustible tobacco.[4]

Electronic cigarettes (ECs) have emerged as an effective harm reduction strategy for individuals who smoke cigarettes who cannot or will not quit using FDA-approved cessation methods.[5] EC are used by one in six US adult cigarette smokers[2, 6] and are now the most common assisted method of quitting cigarettes.[7] Exclusively switching from cigarettes to ECs optimizes harm reduction relative to continued smoking[8-12] and growing evidence indicates that partially switching to EC reduces cigarette consumption, is a marker of EC acceptability, and might also be associated with reduced harm, particularly for cancer and COPD.[10, 13, 14] In our RCT that directly informs the current study, partial switchers replaced > 75% of their cigarettes with EC, resulting in a decrease of 70 cigarettes per week from baseline and significant reductions in the potent lung carcinogen, NNAL, carbon monoxide, and respiratory symptoms.[15] Current estimates indicate that 6.6 million premature deaths could be prevented over the next decade in the US and 86.7 million fewer years of life lost if adult cigarette smokers switched to EC.[5]

Menthol flavoring in cigarettes. Menthol is a flavor additive with a minty taste and aroma that, when added to cigarettes, increases appeal and addictive potential, reduces the irritation and harshness of smoking, leads to greater depth of inhalation of tobacco smoke and its harmful constituents, facilitates dependence, and decreases the likelihood of cessation.[16] Targeted tobacco industry marketing of menthol cigarettes to African American (AA) communities since the 1940s has led to disproportionately higher rates of menthol cigarette use.[17-19] Today, 85% of all AA smokers smoke menthol cigarettes compared to 20% of Whites.[20] Despite similar smoking prevalence, smoking on fewer days, and lower overall levels of daily cigarette consumption,[21-23] AAs are two to three-times more likely to die of tobacco-related illnesses, including cancer and heart disease, than other racial/ethnic groups; [24-26] menthol cigarettes are believed to be a major reason for this disproportionate suffering among AA smokers. Simulation modeling estimated that if the US had implemented a menthol cigarette ban in 2011, 190,000 Black lives and 633,000 deaths, overall, would have been averted by 2050.[27] *The FDA's monumental decision to advance the rulemaking process to ban menthol cigarettes is an important step toward closing the gap in tobacco-related disease and death disproportionately experienced by AA smokers.*

Menthol flavoring in EC. The FDA's regulatory action on April 29, 2021 stopped short of including menthol-flavored ECs and debate continues about whether more comprehensive enforcement priorities inclusive of menthol flavored e-liquids should be enacted. At present, FDA is calling for research that examines the impact of EC flavoring on tobacco use behaviors with a particular focus on possible unintended consequences of tobacco regulatory actions on populations disproportionately burdened with tobacco-related health disparities. *The current proposal directly responds to this call and, to our knowledge, will be the first prospectively designed study to directly compare the efficacy of menthol*

versus tobacco EC at facilitating switching from tobacco cigarettes to EC in adult menthol smokers transitioning to EC. We anticipate enrolling > 80% racial/ethnic minorities (primarily AA and Latinx) into the current study, thereby focusing on the populations who will be most impacted by regulatory action on menthol.

C. Rationale

Innovation in this application lies in the methods applied to the research question and the population studied. The status quo as it pertains to understanding the role of EC flavoring in adult smoker's tobacco use behaviors is to conduct observational and lab-based studies. [35, 37, 38, 40, 41, 45, 46) (42] These designs contribute important information about the association between EC flavors and switching, but they cannot determine causality and are limited by self-selection bias. To definitively answer the question about the efficacy and acceptability of menthol EC versus tobacco EC at facilitating switching in adult smokers, an RCT is needed to establish if the observed associations are due to self-selection or are truly causal. *In that regard, the research proposed in this application is innovative, because it represents a departure from the status quo by being the first RCT to directly compare EC flavoring in adult menthol smokers interested in switching.* Results from our preliminary studies (see C3) suggest comparable rates of switching from tobacco cigarettes to EC, tobacco harm reduction, EC product use, and acceptability between adult menthol smokers who used tobacco EC versus menthol EC and, in doing so, provide compelling evidence for conducting a fully powered RCT comparing menthol and tobacco EC. In addition, racial/ethnic minorities in the US are more likely to smoke menthol cigarettes and will be most impacted by regulatory action on menthol as a characterizing EC flavor, yet these groups are underrepresented in existing observational and lab-based studies examining the role of EC flavoring on adult smoker's tobacco use behaviors. *The research proposed in this application is further innovative, as it represents a departure from the status quo in that we will conduct the largest intervention trial of racial/ethnic minority menthol smokers ever done. We anticipate > 80% representation from racial/ethnic minority groups, primarily AA and Latinx.* Results have the potential to shift paradigms. Specifically, based on our strong preliminary data, we expect that both menthol and tobacco EC will be acceptable and result in high rates of switching and improvements in tobacco-related health effects. The study will provide critical data to the FDA to inform regulatory action of menthol EC that could slow youth and young adult initiation with no resulting negative impact on switching in adult combustible cigarette smokers transitioning to EC and no unintended consequences in a priority population of predominately AA and Latinx smokers.

II. Research Plan and Design

A. Study Objectives

This study will examine the short- and long-term effectiveness, tobacco harm reduction, and acceptability of menthol versus tobacco EC in adult menthol smokers not interested in quitting nicotine but interested in switching from cigarettes to EC.

B. Study Type and Design

Menthol smokers (n=800), stratified by race and gender, who are not interested in quitting nicotine will be randomized 1:1 into a 12-week open label, non-inferiority trial comparing a 4th generation nicotine salt-based pod-system EC in menthol or tobacco flavoring. Each group will be provided a 12-week supply of EC 5% nicotine concentration in either menthol or Virginia tobacco and will complete 4 check-in sessions to facilitate switching to EC. The primary outcome is the proportion who make a complete or predominant switch to EC at week 12, where complete switching is defined as exclusive use of EC, biochemically confirmed with CO < 6, and predominant switching is defined as use of EC with > 50% reduction in CPD. Secondary outcomes include acceptability and long-term effectiveness. Follow-up will continue through week 26 to examine long-term maintenance of EC product use and smoking behavior under naturalistic conditions. Participants will be recruited and enrolled in collaboration with The University of Kansas Health System and Swope Health Central (Swope), a federally qualified health center serving a predominately AA population, that has been the site for our previous trials.

Why a non-inferiority trial? Non-inferiority trials are executed when one product is anticipated to be 'not unacceptably worse than' a comparator product and have value when it is feasible to sacrifice some degree of benefit to gain advantages provided by another product. [53,54] In the case of EC flavoring, the tradeoff of lower efficacy and acceptability of tobacco EC to adult menthol smokers may be well worth the advantages gained in youth and young adult initiation so long as the difference between tobacco and

menthol EC is not so large that adult menthol smokers are unwilling to use tobacco EC. The alternative would be a superiority study, but these are used to conclude that one product is better than the other, and at the time of this proposal there is no data supporting this approach that menthol EC are more effective than tobacco EC at facilitating a switch from tobacco cigarettes to EC or vice versa. Rather, data from our RCT and other studies suggest that tobacco EC are non-inferior to menthol EC in terms of effectiveness and acceptability to adult users, but a fully powered RCT is needed.

C. Sample size, statistical methods, and power calculation

Sample size calculation. The aim of this non-inferiority trial is to establish that tobacco EC are not inferior to menthol EC in terms of the primary outcome, which is the proportion of menthol smokers who make a complete or predominant switch to EC, defined as use of EC along with a > 50% reduction in cigarettes from baseline to week 12. We assume 1) based on our RCT, that 73% in the menthol EC group will be complete or predominant switchers at week 12. We arrived at the 73% estimate at week 12 by examining the trend in switching from week 2 to week 6 in our RCT. Specifically, we noted a 12% reduction in switching from week 2 to week 6 and assumed that a similar trend would continue through week 12. Given an 85% switch rate in the menthol EC group at week 6 in our RCT and assuming a 12% reduction in switching from week 6 to 12, gives us a 73% switch rate at week 12. We also assume 2) to prove non-inferiority, the proportion in the tobacco EC group that are complete and partial switchers at week 12 will be similar to the menthol EC as long as it is greater than 64%. So, we can assume that P1=the proportion in the tobacco EC group that will be complete or predominant switchers at week 12=0.64 and that P2=the proportion in the menthol EC group that will be complete or predominant switchers at week 12=0.73. Then to test for noninferiority we have the following hypotheses: H0 (null hypothesis): P1-P2 $\leq$ -0.09 and H1 (alternative hypothesis): P1-P2 > -0.09. Following these assumptions 400 per group gives us 82% power with a Type 1 error rate of 2.5% using a normal approximation test for non-inferiority. Sample size calculations were done with PASS 16.0.4.
Basis for sample size calculations. Estimates for non-inferiority trials are guided by an effectiveness ratio that indicates how effective one product is relative to another product and is determined from estimates on the outcome of interest and the a priori difference threshold. *The FDA and other regulatory bodies have established an effectiveness ratio of $\geq$ 80% to indicate bioequivalence (i.e., non-inferiority).[132] This is the criterion that we used in determining sample size for this study.* Recent tobacco non-inferiority studies, including a tobacco harm reduction study comparing EC to heat-not-burn, have used a difference threshold of 15%.[133] [134] Using this 15% threshold and our estimate of a 73% complete or predominant switch rate in the menthol EC group gives us an effectiveness ratio of 79% (.58/.73), which is under the criteria set by FDA. Raising the difference threshold to 14% would give us an effectiveness ratio of 81% (.59/.73). While this meets FDA criteria for non-inferiority, we felt that a difference of 14% was too large. Rather, we have gone with a more stringent difference threshold of 9%; at this threshold the proposed effectiveness ratio for our study is 88% (.64/.73), meaning that tobacco EC will be assumed to not be inferior to menthol EC if they are at least 88% as effective at facilitating a complete or predominant switch as menthol EC. This criterion places us well above the equivalence threshold set by the FDA and is more conservative than similar tobacco harm reduction non-inferiority studies, which we believe is a strength of this study. **Missing data.** We expect minimal (<5%) lost to follow-up at week 12 based on our recent studies, however those lost will be considered as non-complete or predominant switcher and will be imputed as such.

Statistical evaluation of study aims

Aim 1. Compare the effectiveness of menthol versus tobacco EC at facilitating switching at week 12. Primary hypothesis. *Participants randomized to tobacco EC (versus menthol EC) will demonstrate non-inferior rates of complete and predominant switching to EC (primary outcome). Complete switching is defined as exclusive use of EC, biochemically confirmed with CO < 6 ppm, and predominant switching is defined as use of EC with > 50% reduction in CPD.* We will test this hypothesis by calculating the 95% confidence interval for the difference in P1-P2, as defined above. To show noninferiority the upper limit of the confidence interval must be greater than or equal to 0.00 and lower limit of the confidence interval must be larger than -0.09. If the upper limit of the confidence interval is less than 0.00 then we cannot conclude noninferiority. If the upper limit is greater than or equal to 0.00 and the lower limit is less than or equal to -0.09 then the results would be inconclusive.
Rates of complete and predominant switching will also be compared separately by group using the chi-square test. Note, that we have not specified an a priori difference threshold for these analyses and, therefore, they are not testing noninferiority and should be considered exploratory. What these analyses will provide is an estimate of the proportion of complete switchers in the tobacco EC versus menthol EC group

and, separately, an estimate of the proportion of predominant switchers in the tobacco EC versus menthol EC group.

Aim 2. Compare tobacco harm reduction of menthol versus tobacco EC at week 12. Hypothesis 2. *Participants randomized to tobacco EC (versus menthol EC) will demonstrate comparable (i.e., no statistically significant differences) change in CO, respiratory symptoms, lung function, blood pressure, and tobacco-related quality of life from baseline to week 12.* Each of these measures are on a quantitative scale and, given the sample size, we can assume the central limit theorem will hold. Thus, we will calculate the mean change and standard deviation of the change for each of these measures from baseline to week 12 by group. We will then conduct the two-sample t-test comparing the means between the groups while also reporting the corresponding 95% confidence intervals. Given that we expect to show noninferiority and comparable effects between groups, we except to fail to reject each of these tests and thus each confidence interval for the difference between groups will contain 0.00. However, if any of these variables are different when noninferiority is seen – i.e., Aim 1 is supported, meaning tobacco EC are found to be non-inferior to menthol EC on rate of switching – we will then utilize logistic regression analyzes to identify any phenotypic or consumption patterns that may predict why these variables differ in the face of noninferiority. For example, we may find that tobacco-related quality of life differs by group even though tobacco EC were found to be noninferior to menthol EC on rate of switching. In this case, factors such as gender, age, socioeconomic status, study-related side effects, adverse events, change in CPD, cigarette-related withdrawal, craving, dependence, EC usage and grams of e-liquid consumed, subjective effects of vaping, baseline smoking history, or psychosocial factors may explain this difference and the regression analyses undertaken will illuminate the potential reasons for the difference. If noninferiority is not seen – i.e., Aim 1 is not supported -- then we expect to see a difference in one or more of these measures.

Aim 3. Compare the acceptability of menthol versus tobacco EC at week 12. Hypothesis 3. *Participants randomized to tobacco EC (versus menthol EC) will consume comparable amounts of study provided e-liquid (measured in grams) and demonstrate comparable reductions in cigarette-related withdrawal, craving, and dependence. Subjective effects of vaping will also be compared between groups.* Each of these measures are on a quantitative scale and, given the sample size, we can assume the central limit theorem will hold. Thus, we will calculate the mean e-liquid consumption over 12 weeks and its corresponding standard deviation by group. We will then compare the difference in these means between the groups using a two-sample t-test and calculate the corresponding 95% confidence interval. Given that we expect to show noninferiority in tobacco EC versus menthol EC, we expect to find no difference in e-liquid consumption and, therefore, the confidence interval for the difference between groups will contain 0.00. If noninferiority is not seen, then we may see a difference in the e-liquid consumption by group. For change in cigarette-related withdrawal, craving, dependence, and subjective effects of vaping, we will calculate the mean change and corresponding standard deviation for each of these measures by group. We will then conduct the two-sample t-test comparing the means between the groups while also reporting the corresponding 95% confidence intervals. Given that we expect to show noninferiority in tobacco EC versus menthol EC, we expect to find no difference in cigarette-related withdrawal, craving, dependence, or subjective effects of vaping. This means that we expect to fail to reject each of the t-tests and expect that each confidence interval for the difference between groups will contain 0.00. However, as described in Aim 2, if any of these variables are different when noninferiority is seen, we will then utilize logistic regression to identify any phenotypic or consumption patterns – e.g., gender, age, socioeconomic status, study-related side effects, adverse events, change in CPD, cigarette-related withdrawal, craving, dependence, EC usage and grams of e-liquid consumed, subjective effects of vaping, baseline smoking history, or psychosocial factors -- may explain this difference and the regression analyses undertaken will illuminate reasons for the difference.
If noninferiority is not seen, then we would expect to see a difference in one or more of these measures.

Aim 4. Examine the long-term effectiveness of menthol versus tobacco EC at week 26. We will compare switching patterns at week 26 to examine long-term maintenance of EC and smoking patterns under naturalistic conditions (EC only provided up to week 12). **Hypothesis 4.** *There will be no statistically significant difference in rates of complete or predominant switching at week 26 between those randomized to menthol versus tobacco EC.* For this aim we will calculate the proportion of complete and predominant switchers as defined above but at week 26. We will then calculate the corresponding 95% confidence interval on the difference in these proportions. The lost to follow-up rate at month 6 in the RCT that forms the basis for this proposal was < 10%. We do not expect the lost to follow-up rate to exceed 20% at month 6; however, given that we are not sure of our loss to follow-up rate we will report complete and

predominant switching at month 6 assuming those lost are not complete or predominant switchers and subsequently report on completers only.

D. Subject Criteria (See Vulnerable Populations appendix, if applicable)

Participants will be adults 21 years or older who smoked at least 5 cigarettes daily at enrollment and have smoked menthol cigarettes for ≥ 6 months. The study will be open to both men and women.

Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• ≥ 21 years of age • Smoke ≥5 CPD • Smoked menthol cigarettes for ≥ 6 months • Verified smoker (CO ≥ 5 ppm) • Functioning telephone • Interested in switching to EC	• Interested in quitting smoking • Use of other tobacco products in past 30 days (i.e., cigarillos, cigars, hookah, smokeless tobacco, pipes) • EC use on ≥ 4 of the past 30 days • Uncontrolled hypertension: BP ≥ 180 (systolic) or ≥ 105 (diastolic) • Use of smoking cessation pharmacotherapy in the month prior to enrollment • Pregnant, contemplating getting pregnant, or breastfeeding • Plans to move from KC during the treatment or follow-up phase • Another household member enrolled in the study

Inclusion criteria

Inclusion criteria are displayed in the adjoining table. Eligible individuals must be at least 21 years, interested in switching to EC, smoked ≥5 cpd, smoke menthol cigarettes for ≥6 months, be a verified smoker (CO ≥ 5PPM), be willing to complete all visits, and have a functioning telephone number.

Exclusion criteria

Exclusion criteria are also displayed in the adjoining table. Individuals who are interested in quitting smoking will be excluded and referred to smoking cessation resources. Other exclusions include individuals who have used EC on at least 4 of the past 30 days, uncontrolled hypertension (BP ≥ 180 (systolic) or ≥ 105 (diastolic)), anticipated or current pregnancy (as measured by over-the-counter pregnancy test kit for women of childbearing age only), breast feeding. Other exclusions include use of stop smoking medications in the past 30 days, daily use of other nicotine or tobacco products, plan to move from the Kansas City area in the next year, or other smoker in household enrolled in the study.

Withdrawal/Termination Criteria

There are no expected circumstances in which the subject's participation will be terminated by the investigator.

Clarify whether a study subject may participate in another research study while participating in this research study

Subjects are not able to participate in a smoking cessation research study while they are enrolled in the current study.

E. Specific methods and techniques used throughout the study

Laboratory tests

Not more than 20 ml of urine and saliva will be collected at Weeks 0, 12 and 262. The urine and saliva will be banked for future analyses.

Study Procedures:

Intervention

All eligible participants who provide written informed consent and complete the baseline survey will be randomized in a 1:1 fashion to either menthol or Virginia tobacco EC.

Treatment Overview.

Randomization. All eligible participants who provide written informed consent and complete the baseline survey will be stratified by race and gender and randomized 1:1 to either menthol or Virginia tobacco EC. Randomization will be determined by computer-generated random numbers. Randomization assignments will be placed in sealed envelopes with sequential study ID numbers. After baseline data collection has been completed, the research assistant will select the sequential study ID number to determine the randomization assignment.

EC (Weeks 0-12). Participants will be provided a 12-week supply of VUSE 5% nicotine concentration in either menthol or Virginia tobacco that will be dispensed at the weeks 0, 4, and 8 in-person visits (4-week supply @ each visit). One pod delivers the equivalent of one pack of cigarettes, with variability of 13-30 cigarettes based on user, [77] and therefore allocation will be based on 1 pod per pack of cigarettes at week 0 and on current use patterns at weeks 4 and 8.

EC use. Participants will be instructed to use only the study EC in the flavor provided but to report all ECs by timeline follow-back at follow-up visits. To aid in recall and assessment of fidelity to protocol, participants will be given dated bags to collect all EC. Bags will be returned at each visit during the intervention phase to confirm use of EC (i.e., grams of e-liquid consumed and count of pods) as well as protocol adherence (i.e., the number of pods/grams vaped in the study provided versus non-study provided flavor) (see Measures). Those not attending EC dispensing visits will be reached by phone and delivered enough to get them to the next dispensing time point. Participants will be compensated for returned pods, but earnings will not be tied to protocol adherence. Participants will be paid for returned pods even if they return non-study provided EC to increase honest reporting.

EC Check-in: Participants will be provided brief education and advice on benefits of switching to EC at baseline (week 0), followed by in person check-ins at weeks 4, 8, and 12 to monitor EC use. They will also complete weekly calls during the first month to encourage adoption of the EC and ensure that participants have sufficient supply. Check-in sessions will be conducted by our experienced staff, who are certified tobacco treatment specialists, have extensive experience treating racially/ethnically diverse smokers within clinical trials, and are active members of the community. Drs. Cox and Leavens, co-Is and clinical psychologists, will be responsible for staff training and supervision, as they have done over the past 20 years for over 6 clinical trials**.** Each session will last approximately 15-30 minutes.

Procedures and Methods

An overview of major study events is provided in the adjoining table.

	Screen*	Enroll						Primary Outcome		
		▫Wk 0	Wk 1*	Wk 2*	Wk 3*	Wk 4	Week 8	Wk 12	Wk 18	Week 26
Remuneration		$40				$60	$60	$60	$40	$40
EC Check-ins		X	X	X	X	X	X	X		
Dispense EC		X				X	X	X		
Screening	X	X								
Consent		X								
Assessments		X				X	X	X	X	X
Spirometer		X						X		X
CO		X				X	X	X	X	X
Blood Pressure		X						X		X
Exhaled Breath Condensates		X				X	X	X		
Urine and Saliva		X						X		X

* Over the phone

Initial Screening. The initial screen will review inclusion/exclusion criteria. Those eligible will be scheduled to complete final eligibility screening within 21 days. All ineligible smokers will be referred to local resources when applicable.

Final Screening and Enrollment (Wk 0). Final eligibility screening will be conducted in person and will consist of a pregnancy test on women of childbearing age and obtaining informed consent.

Electronic cigarettes (Wk 0, 4, 8, 12). Participants will be provided a 12-week supply of VUSE 5% nicotine concentration in either menthol or Virginia tobacco that will be dispensed at the weeks 0, 4, and 8 in-person visits (4-week supply @ each visit). To aid in recall and assessment of fidelity to protocol, participants will be given dated bags to collect all EC. Bags will be returned at each visit during the intervention phase to confirm use of EC (i.e., grams of e-liquid consumed and count of pods) as well as protocol adherence.

EC Check-in Visits (Wks 0, 4, 8, and 12). Check-in sessions, each lasting approximately 20 minutes, will be completed in person at Wks 0, 4, 8, and 12 and by phone at Weeks 1, 2, and 3. The number of sessions is consistent with our previous studies where we have achieved visit completion rates of ~ 80%.[12,14,15,19]

Spirometer. Lung function will be assessed via spirometry. We will carefully monitor respiratory symptoms over time using standardized measures. Spirometry will be completed at Wks 0, , 12, and 26.

Carbon Monoxide. Exhaled air carbon monoxide (CO) is an immediate, non-invasive method of biochemically verifying smoking status. At Wks 0, 4, 8, 12, 18, and 26, all participants will breathe into a Micro-3 Smokerlyzer (Bedfont Scientific) for the purpose of determining smoking levels.

Blood Pressure. Systolic and diastolic blood pressure will be measured with an Welch Allyn blood pressure cuff at Wks 0, 12, and 26.

Exhaled breath condensates (EBC). EBC will be used as another mean to assess airway inflammation. EBCs will be collected using the RTube (Respiratory Research, Inc.). Subjects will breathe in and out through a mouthpiece at tidal volume. A one-way valve will direct the exhaled air through the cooling sleeve where the samples are collected. The collection time will be 10 minutes. Typical condensate fluid yield is 300 µl/minute for an adult at normal tidal breathing effort. The EBC will be stored in 1 ml aliquots at -80°C for subsequent analysis. Samples will be standardized by total collected volume. EBC will be used to measure inflammatory patterns using nanobiosensors.

Retention. Retention is enhanced by having participants meet with the same study team member each time. We have also developed a system of reminders and compensation for participant efforts that have resulted in impressive retention rates in our previous clinical trials. Reminders. Five days prior to each visit a reminder postcard, email, and/or text noting the scheduled appointment date and time will be sent. Participants will also be called, texted, or emailed (based on preference) up to 6 times to remind them of their upcoming visit. A detailed tracking database, with an automated reminder system, will notify study staff of when to send reminder messages. Compensation. Participants will be compensated in the form of a ClinCard, which works like a debit card. They will receive $40 at Wks 0, 4, 8, 18, and 26 and $50 at Week 12 as compensation for their time/travel. To encourage use of the study provided EC, an additional $20 will be provided at weeks 4, 8, and 12 for returning EC pods, regardless of the flavor returned.

Clearly indicate which procedures, tests, visits, etc., are parts of usual standard therapy and which are performed solely for research purposes.

All tests, procedures, and visits are being performed solely for research purposes and are not billable to insurance companies.

Describe the fate of any body component (blood, CSF, bone marrow, etc.) used in the study, emphasizing confidentiality of labeling of the sample and the sample's destruction or storage.

Samples will be labeled only with a unique study identification number and only members of Dr.

Nollen and Toren's team will have access to the samples. For participants who have agreed to have their biospecimens stored for future testing, samples will be stored indefinitely.

F. Risk/benefit assessment

Physical risk
The most common side effects related to EC include cough, dry mouth, shortness of breath, mouth and throat irritation, headache, dizziness, nausea or vomiting, and increased heart rate/palpitations. In rare instances, severe pulmonary disease associated with EC use and death have been noted, but these incidents have primarily occurred in a black-market product that contained tetrahydrocannabinol, or THC, in combination with vitamin E acetate. These additives are not present in the EC used in this study.

Psychological risk
Risks for participants also include those associated with the inconvenience of participation including answering surveys, providing saliva, urine, and participating in follow-up visits and assessments. To minimize the inconveniences associated with study participation we will review all data collection instruments and study procedures to minimize the number of items in our instruments and improve the accessibility and convenience of our study procedures. We anticipate using several methods to enhance convenience to participants, including offering study visits in the evening and on weekends and offering patients a choice of where they will be seen (KUMC or Swope). Another risk is feeling pressured to be in the study, which we will track in order to monitor and will report this as an adverse event.

Social risk
None

Economic risk
None

Potential benefit of participating in the study
There are also no direct benefits to participating in this study except that researchers hope that the information from this research study may be useful in informing the FDA's regulatory action on menthol flavoring in EC.

G. Location where study will be performed:

The study will take place at The University of Kansas Tobacco Treatment Center at Swope, 4001 Dr. Martin Luther King Jr. Blvd, in Kansas City, Missouri (hereafter referred to as Swope) or at the KUMC CRU in Fairway, Kansas based on the preference of each participant. All data will be directly entered into an electronic data capture system (i.e., RedCap or CRIS), therefore minimizing the use of paper records. If paper records are generated, they will be stored in locked file cabinets at Swope. Only study staff will have access to the locked records at Swope and the secure online electronic data capture system.

H. Collaboration (with another institution, if applicable): N/A

I. Single IRB Review for a Multi-site study (if applicable): N/A

J. Community-Based Participatory Research (if applicable): N/A

K. Personnel who will conduct the study, including:
Indicate, by title, who will be present during study procedure(s)
Personnel on the project include: Nicole L. Nollen (PI), Lisa Cox (Co-I), Eleanor Leavens (Co-I), Matt Mayo (co-I, lead biostatistician), Tricia Snow (project director), Alexandra Brown (senior research analyst), Dinesh Pal Mudaranthakam, (clinical information specialist), Leah Lambart (Graduate Research Assistant), Drennon 'Kris' Leverette (Graduate Research Assistant), and Terri Tapp (research assistant).

1. Primary responsibility for the following activities, for example:

    a. *Determining eligibility:* Tricia Snow, Terri Tapp, Leah Lambart, Olivia Funk, Anetra Hunter, Brian Hernandez, Sophia Jumani
    b. *Obtaining informed consent:* Tricia Snow, Terri Tapp, Leah Lambart, , Olivia Funk, Anetra Hunter, Brian Hernandez, Sophia Jumani
    c. *Providing on-going information to the study sponsor and the IRB:* Nicole Nollen, Tricia Snow

    d. *Maintaining participant's research records:* Tricia Snow, Terri Tapp, Leah Lambart, , Alexandra Brown, Dinesh Pal Mudaranthakam, Matt Mayo

    e. *Completing physical examination:* Not applicable

f. Taking vital signs, height, weight: Height and weight will be the only vital signs taken. They will be performed by Tricia Snow, Terri Tapp, Leah Lambart, Olivia Funk, Anetra Hunter, Brian Hernandez, Sophia Jumani.

    g. *Drawing / collecting laboratory specimens:* Tricia Snow, Terri Tapp, Leah Lambart, Olivia Funk, Anetra Hunter, Brian Hernandez. KUMC Study staff will be handling and storing the samples.

    h. *Performing / conducting tests, procedures, interventions, questionnaires:* Tricia Snow, Terri Tapp, Leah Lambart, Olivia Funk, Anetra Hunter, Brian Hernandez, Sophia Jumani

    i. *Completing study data forms:* Tricia Snow, Terri Tapp, Leah Lambart, Olivia Funk, Anetra Hunter, Brian Hernandez, Sophia Jumani
    j. *Managing study database:* Matt Mayo, Alexandra Brown, Dinesh Pal Mudaranthakam, Tricia Snow

L. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

The current study involves an EC that is publicly marketed and commercially available for purchase to anyone over the age of 21. ECs are a tobacco product and are being provided for non-therapeutic purposes. ECs are no more harmful than conventional cigarettes, and various studies suggest that they may offer reduced harm.

This study does not involve more than minimal risk. We will protect participants and minimize risks by using the strict exclusion criteria and careful monitoring of adverse events (AEs). AEs will be tracked during regularly scheduled visits or through spontaneous reports made by participants. Dr. Nollen will be made aware of unexpected or serious AEs within 24 hours of the first report by participants; all other AEs will be reviewed weekly by Dr. Nollen. SAEs will be reported to the KUMC IRB, FDA, and NIDA within 24 hours of first awareness of the event. Unexpected adverse events that are related to the study medication will be reported to KUMC IRB, FDA, and NIDA within 5 working days of first awareness of the event if the event is not serious fatal and within 24 hours of first awareness if the event is serious. Unexpected adverse events that are unrelated to the study medication will be reported to the KUMC HSC during yearly routine event reporting. IRB actions taken in this study will be reported to NIDA. Dr. Greiner (or the treating provider) will determine relatedness for each reported AE. SAEs will be defined as any event experienced by a study subject while on the study medication that is fatal, life-threatening (subject was at risk of death from the event as it occurred), disabling or incapacitating, requires inpatient hospitalization or prolongs a current hospitalization, is a congenital anomaly in the offspring of a subject who received the study medication, or required intervention to prevent permanent impairment or damage.

III. Subject Participation

A. Recruitment:

Participants will be recruited through clinic and community-based efforts. Flyers will be placed around Swope and KUMC for patients to take and providers will be asked to refer patients by providing them with the study line information. We will use the KUMC HERON database and the Swope electronic medical records to identify smokers and will ask their physician to send their patient a letter informing them of the study. We will also use the Frontiers registry to identify adult smokers who have agreed to be contacted for research. We will use radio, TV, bus and Facebook ads and word of mouth, as needed, to recruit participants. Finally, smokers are currently being screened for other research studies being conducted by our team (i.e., active studies being conducted Drs. Nollen, Cox, or Leavens). Those who are found to be ineligible for these studies will be informed about the current study and offered the opportunity to be screened. Recruitment letters, advertisements, and flyers are in the process of being developed. They will be submitted to the IRB for approval before any participants are enrolled.

B. Screening Interview/questionnaire

The screening interview will take place over the phone or in person and be conducted by a member of the study team. The screening questionnaire will address the general inclusion/exclusion criteria in the Eligibility Criteria table above. Only participants who have expressed interest will be screened.

C. Informed consent process and timing of obtaining of consent

Consent will be obtained prior to participant involvement. Individuals interested in the proposed study will meet the research assistant at Swope or the CRU. Each individual will be given a copy of the consent form and as much time as they need to review its contents. After the consent form is read, both the individual and the research assistant will review the consent form together and the potential participant will be encouraged to ask questions. Each individual will be reminded that participation in the study is completely voluntary and their decision to participate will not affect their current or future medical care at the treating facility**.** The consenting process will take place in a private location.

D. Alternatives to Participation

Alternatives to participating in the study are continue to smoke cigarettes as usual or switch to other alternative sources of nicotine, including purchasing nicotine gum or patches from the pharmacy or obtaining a prescription for nicotine inhaler, nicotine nasal spray, or nicotine lozenge.

E. Costs to Subjects

There are no costs to subjects. All tests, procedures, and visits are being performed solely for research purposes and are not billable to insurance companies.

F. How new information will be conveyed to the study subject and how it will be documented

We have plans to publish data from this study in aggregate but will not provide any individualized feedback to participants.

G. Payment, including a prorated plan for payment

Participants will be given a $40 electronically loaded ClinCard at Wks 0, 4, 8, 12,18, and 26 as compensation for their time/travel. To encourage use of the study provided EC, an additional $20 will be provided at weeks 4, 8, 12 visits for returning EC pods, regardless of the flavor returned. Participants must complete the visit to receive the reimbursement associated with that time point. Participants may receive $20 for each referral who is eligible and enrolls in the study. Participants may complete up to 3 different referrals for the study for a total of $60. Travel costs will not be reimbursed.

H. Payment for a research-related injury

N/A

IV. Data Collection and Protection

A. Data Management and Security

Confidentiality will be maintained by assigning each participant a study identification number and numerically coding all data. The association of the ID-code and the participant's name will be kept by Tricia Snow in a locked file cabinet. The screening questionnaire and all survey data will be directly entered into RedCap or CRIS and accessible only by study staff. Any paper copies of records will be kept in a locked filing cabinet in offices that are kept locked when unoccupied. Only summaries of group data will be reported in any publications or presentations, with no identification of individuals. Because identifiable information will be collected, participant privacy will be maintained throughout the duration of the study by adhering to the regulations set forth by the HIPAA Privacy Rule. More specifically, identifiable information will not be released without written authorization of the participant. Mobile devices will not be used for data collection or storage. Identifiable data will not be sent outside of KUMC.

B. Sample / Specimen Collection

No more than 20 ml of urine and saliva will be collected at Weeks 0, 12 and 26. Samples will be stored at the Bioanalytical Laboratory at the Fairway Clinical Research Center under the direction of Paul Toren, PhD. Samples will be accessible only to members the study team. Results from analyses will be de-identified and shared only with members of the research team. Any resulting publications will present the data in aggregate; individual participants will not be identified. For participants who agree to future testing, samples will be stored indefinitely.

C. Tissue Banking Considerations

For participants who agree to future testing, samples will be stored indefinitely. New biomarkers of tobacco-related harm and exposure and genetic differences in nicotine metabolism are being discovered and the stored biological samples would be used for analysis of these new markers. All samples stored for future biomarker analyses will be de-identified and accessible only to members of the study team. Results from these analyses will be de-identified and shared only with members of the research team. Any resulting publications will present the data in aggregate; individual participants will not be identified.

D. Procedures to protect subject confidentiality

Confidentiality will be maintained by assigning each participant a study identification number and numerically coding all data. All biological samples and survey data will be labeled with the study identification number and never with the participants name or other identifiable information. The association of the ID-code and the participant's name will be kept by Tricia Snow in a locked file cabinet and will only be accessible to members of the study team.

E. Quality Assurance / Monitoring

All data will be directly entered into our electronic data capture system (i.e., RedCap or CRIS) that contains edit checks to control the quality and completeness of data entry. Completeness of data entry will be automatically verified before each assessment is completed. The electronic data capture system is behind the KUMC secure firewall with role-based access that is HIPAA and human subjects compliant. There are no plans for ongoing third-party monitoring.

V. Data Analysis and Reporting

A. Statistical and Data Analysis

See II.C. above (Sample Size, Statistical Methods, and Power Calculations)

B. Outcome

EFFECTIVENESS (Aims 1 & 4).

Switching (Primary Outcome). The primary outcome is the proportion of menthol smokers who make a complete or predominant switch to EC, defined as use of EC along with a > 50% reduction in cigarettes from baseline to week 12. The **7-day Timeline Follow Back Interview (TLFB)** will be used to assess participants cigarette and EC use patterns each day for the past 7 days at each visit (weeks 0, 4, 8, 12, 18, 26). The primary endpoint is, however, fixed at week 12. The TLFB is a reliable and valid way of collecting information about substance use quantity and frequency and, in tobacco research, has been corroborated against interactive voice response, butt counts (storing and returning the butts of cigarettes smoked), and biological measures for cigarettes smoked and puff topography for EC, supporting the strong validity of this self-report measure compared to other 'gold standard' measures. For each of the last 7 days participants will be asked to recall the number of cigarettes smoked and EC sessions vaped; following standard practice, an EC session is defined as at least 15 puffs or lasting around 10 minutes. For each EC session, participants will be asked to specify the device used (i.e., study provided versus something else) and the flavor (i.e., menthol, Virginia tobacco, something else).* For non-study provided EC, detailed information will be collected about the type of EC (e.g., brand, pod-based, disposable, refillable), flavor, nicotine concentration and, if available, whether the product is nicotine salt-based. To aid in recall and corroborate self-report, participants will be given dated bags to collect all EC. Bags will be returned at each visit during the intervention phase and used to confirm use of study provided EC (i.e., grams of e-liquid consumed) and protocol adherence (i.e., the number of pods vaped in the study provided versus non-study provided flavor). *Complete switching* is defined as any use of EC and no use of cigarettes in the past 7 days (i.e., 100% reduction in CPD from baseline), biochemically confirmed with an expired breath CO < 6 parts per million (ppm). CO is used for verification because cigarettes produce carbon monoxide as a byproduct of combustion, while heating an e-liquid does not generate CO. The < 6 ppm CO cutoff is more conservative than the $\leq$ 10 ppm cutoff that is commonly used and reflects the current state of knowledge for detecting recent cigarette smoking. *Predominant switching* is defined as those who report any use of EC along with a > 50% reduction from baseline in CPD. A > 50% reduction has been selected because it is a measure of acceptability of the EC products and is associated with substantial reductions in biomarkers of harm and exposure relative to continued smoking and is a common endpoint used in tobacco harm reduction studies. *Partial switching* will be defined as those who report any use of EC along with a $\leq$ 50% reduction from baseline in CPD. *No switching (i.e., exclusive cigarette user)* will be defined as those who reported no use of ECs and any use of cigarettes in the past 7 days. A potential fourth group, *no use of e-cigarettes or combustible cigarettes***,** may occur. For all switching trajectories, use of EC will be corroborated with pod counts and objectively measured EC pod weights during the intervention phase.

Other outcomes of interest include tobacco harm reduction and EC acceptability. These constructs may be measured by the following:

TOBACCO HARM REDUCTION (Aim 2). Tobacco harm reduction is a global topic of interest among those transitioning from cigarettes to EC and is largely driven by reduction in CPD. We expect comparable rates of switching between groups and, therefore, comparable rates of tobacco harm reduction, defined as change in each of the following constructs from baseline to week 12.

- *Tobacco Quality of Life Impact Tool (TQOLIT™v1)* will be used to assess was used to assess the impact of smoking/vaping on health-related quality of life.
- *Carbon Monoxide.* Carbon monoxide will be measured in parts per million (PPM) using a coVita Bedfont Micro+ Smokerlyzer at each study visit.
- *Blood Pressure.* Systolic and diastolic blood pressure will be measures with an Welch-Allyn blood pressure cuff.
- *Respiratory symptoms* have emerged as a primary concern among EC users and, therefore, we will carefully monitor respiratory symptoms over time using the following standardized measures:

- Lung function will be assessed via spirometry**.** We will summarize all values returned from the spirometer (i.e., FVC, FEV1, FEV1/FVC%, PEF) but will focus our attention on *FEF 25-75%,* the pulmonary function test of small airway disease that is most sensitive to effects of cigarette smoking.
- *American Thoracic Society Questionnaire* (ATSQ) will be used to assess common respiratory symptoms (e.g., cough first thing in the morning, wheezing, shortness of breath, etc.). This measure was selected because it contains items relevant to acute respiratory effects experienced by some cigarette smokers when they initiate EC.
- *Leicester Cough Questionnaire* (LCQ) is a valid, repeatable measure of chronic cough which is responsive to change, especially the onset of cough in established cigarette smokers when they initiate EC.

It is not within the scope or budget of this study to examine additional biomarkers of exposure or potential harm, but we will collect urine and saliva samples from all participants at weeks 0 and 12 and bank them for future analyses. Potential biomarkers of interest have been selected to align with other studies and because they represent categories of toxicants commonly found in tobacco products and tobacco smoke that have been classified by the FDA as contributing to respiratory, cardiovascular, and cancer-related diseases associated with smoking.

Biomarkers of interest include:

- cotinine
- total NNAL (for nicotine-derived nitrosamine ketone - NNK);
- 2-hydroxyethylmercapturic acid (HEMA) (for ethylene oxide);
- 2-hydroxy-3-butenyl-mercapturic acid and isomers (MHBMA) (for 1,3-butadiene);
- 3-hydroxy-1-methyl propyl-mercapturic acid (HMPMA) (for crotonaldehyde);
- 3-hydroxypropylmercapturic acid (3-HPMA) (for acrolein);
- S-phenylmercapturic acid (S-PMA) (for benzene);
- 2-cyanoethylmercapturic acid (CEMA) (for acrylonitrile);
- 2-hydroxypropylmercapturic acid (2-HPMA) (for propylene oxide)
- pyrene (1-OHP)
- matrix metalloproteinaise-8 (MMP8) and interleukin-9 (IL9) for airway epithelial cell inflammation
- 8-Epi-prostaglandin F2α (oxidative stress)
- 11-Dehydrothromboxane B2 (platelet activation)
- soluble intercellular adhesion molecule-1 (sICAM)

ACCEPTABILITY (Aim 3). Detailed assessment of EC product use, effects on withdrawal, craving, and dependence, and subjective and sensorial effects will be evaluated at all study visits to compare acceptability by group (menthol versus tobacco EC).

Grams of study e-liquid consumed (weeks 4, 8, 12). Use of the study EC in the flavor provided will be objectively measured by asking participants to bring all used, unused, or partially used pods to the weeks 4, 8, and 12 study visits. Pods will be weighed prior to their distribution and then upon return to derive *total grams of study e-liquid in the flavor provided consumed* from weeks 0-12. In our RCT, 95%, 92%, and 98% of participants returned their pods at weeks 2, 4, and 6, respectively, and there was no evidence of cheating – i.e., returned pods were in the flavor provided by the study -- suggesting that participants used only the study provided pods throughout the intervention phase. For unreturned pods, we will conservatively assume 0 grams of e-liquid consumed. Objective measurement of pod weights was strongly correlated with number of e-cigarette sessions per day measured by TLFB in our RCT ($r=0.58$, $p < .001$).

Flavor usage (all visits). Based on our RCT, we expect low rates of non-study EC product use, but we will conduct rigorous assessments of adherence to EC flavoring during the intervention phase and continued use during the long-term follow-up phase. From the TLFB, we will summarize the proportion of total EC that were in the study provided versus a non-study provided flavor. From pod counts, we will summarize the number of pods returned by flavor (i.e., menthol, Virginia tobacco, other) and derive an estimate of the proportion of total pods returned that were in the study provided flavor (versus non-study provided flavor).

Craving (all visits). Craving for cigarettes will be assessed using the *Questionnaire on Smoking Urges-Brief* **(QSU)** and its companion, the *Questionnaire on Vaping Craving-Brief (QVC)* will be assessed at each visit and compared between groups**.** Both measures yield a total score and two factor scores: desire to smoke/vape and intention to smoke/vape. The QVC yields a third factor, positive outcome of vaping.

Withdrawal (all visits).The *Minnesota Tobacco Withdrawal Scale*will be used to rate eight withdrawal symptoms in the past 24 hours: anger, anxiety, concentration, craving, hunger, sadness, and sleep. Items are rated from 1 (strongly disagree) to 5 (strongly agree). Scores will be summarized overall and for each construct.

Dependence (all visits). Following guidance from the TCORS dependence workgroup, we will include a compendium of dependence measures, validated for use in assessing both cigarette and EC related dependence, to cover all components of dependence (i.e., quantity and frequency of use, tolerance, perceived benefits, withdrawal symptoms, cravings/urges to use, use despite harm, impaired control, automaticity, preferred over competing rewards, and sensory dependence.) We have intentionally selected cigarette dependence measures that have parallel EC dependence measures to allow for direct comparison in dependence across products by group. These measures include:

- *Patient Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank* [107-109] and its companion the *E-Cigarette Dependence Scale***.**
- *Penn State Cigarette Dependence Index* (PS CDI) and its companion the *Penn State Electronic Cigarette Dependence Index* PS ECDI)
- *Wisconsin Inventory of Smoking Dependence Motives (WISDM)* and its companion the *E-Cigarette Wisconsin Inventory of Smoking Dependence Motives (eWISDM).* Dependence will be summarized for the WISDM total score as well as the average score on the Primary Dependence Motives (i.e., Automaticity, Loss of Control, Craving, and Tolerance.
- *Time to First Cigarette* and *Time to First EC of the Day***.** This single item from the Fagerstrom Cigarette Dependence Scale is the best indicator of dependence in a sample of mostly light smokers ($\leq$ 10 CPD).

Subjective effects of vaping (all visits). The 12-item *Modified Cigarette Evaluation Scale* adapted for e-cigarettes will be administered at all time points to access product satisfaction and subjective and sensorial effects of vaping by group (menthol versus tobacco EC). Questions are answered on 7-point scale from 1 (not at all) to 7 (extremely) and assess *vaping satisfaction (*was vaping

satisfying, did the e-cigarette taste good, did you enjoy vaping), *enjoyment of respiratory tract sensations (*did you enjoy the sensations in your throat and chest), *psychological reward (*did vaping calm you down, did vaping make you feel more awake, did vaping make you feel less irritable, did vaping help you concentrate), *craving reduction* (did vaping immediately relieve your craving for a cigarette), and *aversion (*did vaping make you dizzy, did vaping make you nauseous). The single item, "Did the e-cigarette taste good?" will be used as a proxy for flavor liking as has been done in previous studies. The 23-item *Sensory E-cigarette Expectancies Scale,* particularly the subscales related to taste/smell ('I like the taste of vaping', 'I like the smell of vaping,' 'I like the flavor of vaping') and pleasure/satisfaction ('I like how vaping makes me feel good physically,' 'I like the feeling of satisfaction that I get from vaping') will be administered for secondary assessment of product satisfaction and acceptability.

OTHER CONSTRUCTS OF INTEREST

Safety and tolerability

- *Side Effects.* A symptoms checklist will be used to assess participants experience (yes/no) of common smoking/vaping related side effects, including cough, dry mouth, shortness of breath, mouth and throat irritation, headache, dizziness, nausea or vomiting, and increased heart rate/palpitations. For each side effect reported, participants will be asked whether they attribute the side effect to cigarettes, EC, or both.
- *Safety.* Adverse events observed or reported will be recorded at each in-person visit. Assessments as to seriousness, severity, and the relationship to treatment and other causes will be made. Serious adverse events will also be captured in the centralized database. AEs and SAEs will be reported to the appropriate regulatory agencies.

Descriptive measures *(Week 0)*

- *Demographic variables* include gender, age, marital/cohabitation status, socioeconomic status, psychiatric history, depressive symptoms (PHQ-9), and symptoms of generalized anxiety (GAD-7).
- *Psychosocial variables* include individual- (federal poverty level, financial strain, home ownership, housing stability) and area-level socioeconomic disadvantage (neighborhood social cohesion and trust, safety, and incivilities), race consciousness, experiences of discrimination, perceived stress, resilience, and history of trauma (i.e., adverse childhood experiences). These factors influence differences in smoking outcomes in racial/ethnic minority and socioeconomically disadvantaged smokers and were chosen for that reason.
- *Cigarette use history* will include cigarettes per day, age when started smoking regularly, length of time as a smoker, number of 24 hour quit attempts in the last year, length of the longest quit attempt, other smokers/vapers in the home, smoking/vaping status of partner and five best friends/family members.

C. Study results to participants

Study results will not be shared with participants.

D. Publication Plan

We plan to publish results in appropriate tobacco journals – e.g., JAMA, JNCI, Journal of General Internal Medicine, Addiction, Annals of Behavioral Medicine, Nicotine & Tobacco Research, Cancer Epidemiology, Biomarkers, & Prevention.

VI. Bibliography / References / Literature Cited

1. American Cancer Society. Cancer Facts & Figures for African Americans 2016-2018. 2016; https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-facts-and-figures-for-african-americans/cancer-facts-and-figures-for-african-americans-2016-2018.pdf.

2. NCI. A Socioecological Approach to Addressing Tobacco-Related Health Disparities. . In: Services. USDoHaH, ed. *National Cancer Institute Tobacco Control Monograph 22.* Vol NIH Publication No. 17-CA-8035A. Bethesda, Maryland: National Cancer Institute; 2017.

3. Stead LF, Koilpillai P, Fanshawe T, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. . *Cochrane Database of Systematic Reviews* 2016(3).

4. Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. In: Services DoHaH, ed. Rockville, MD: U.S. Department of Health and Human Services; 2008.

5. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet (London, England).* 2016;387(10037):2507-2520.

6. Jamal A, King B, Neff L, Whitmill J, Babb S, Graffunder C. Current Cigarette Smoking Among Adults — United States, 2005–2015. *MMWR Morb Mortal Wkly Rep* 2016;65(44):1205-1211.

7. Haiman CA, Stram DO, Wilkens LR, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. *New England Journal of Medicine.* 2006;354(4):333-342.

8. Cunningham TJ, Croft JB, Liu Y, Lu H, Eke PI, Giles WH. Vital Signs: Racial Disparities in Age-Specific Mortality Among Blacks or African Americans - United States, 1999-2015. *MMWR Morb Mortal Wkly Rep.* 2017;66(17):444-456.

9. Trinidad DR, Perez-Stable EJ, Emery SL, White MM, Grana RA, Messer KS. Intermittent and light daily smoking across racial/ethnic groups in the United States. *Nicotine and Tobacco Research.* 2009;11(2):203-210.

10. Schoenborn CA, Adams PF, Barnes PM, Vickerie JL, Schiller JS. Health behaviors of adults: United States, 1999-2001. *Vital Health Stat 10.* 2004;219:1-79.

11. Luoto R, Uutela A, Puska P. Occasional smoking increases total cardiovascular motality among men. *Nicotine & Tobacco Research.* 2000;2:133-139.

12. Garfinkel L, Stellman S. Smoking and lung cancer in women: findings in a prospective study. *Cancer Res.* 1988;48:6951-6955.

13. Schane RE, Ling PM, Glantz SA. Health effects of light and internittent smoking: A review. *Circulation.* 2010;121(13):1518-1522.

14. Bjartveit K, Tverdal A. Health consequences of smoking 1-4 cigarettes per day. *Tobacco Control.* 2005;14(5):315-320.

15. Okuyemi KS, Pulvers KM, Cox LS, et al. Nicotine dependence among African American light smokers: a comparison of three scales. *Addictive behaviors.* 2007;32(10):1989-2002.

16. Bronars CA, Faseru B, Krebill R, et al. Examining Smoking Dependence Motives among African American Light Smokers. *J Smok Cessat.* 2015;10(2):154-161.

17. Ayanian JZ, Cleary PD. Perceived risks of heart disease and cancer among cigarette smokers. *Jama.* 1999;281(11):1019-1021.

18. Savoy E, Reitzel LR, Scheuermann TS, et al. Risk perception and intention to quit among a tri-ethnic sample of nondaily, light daily, and moderate/heavy daily smokers. *Addictive behaviors.* 2014;39(10):1398-1403.

19. Fish LJ, Pollak KI, Scheuermann TS, Cox LS, Mathur C, Ahluwalia JS. Comparison of native light daily smokers and light daily smokers who were former heavy smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2015;17(5):546-551. PMID:25180075.

20. Shiffman S. Light and intermittent smokers: Background and perspective. *Nicotine & Tobacco Research.* 2009;11(2):122-125.

21. Sakuma KK, Felicitas-Perkins JQ, Blanco L, et al. Tobacco use disparities by racial/ethnic groups: California compared to the United States. *Preventive medicine.* 2016;91:224-232.

22. Castro FG. Physiological, psychological, social, and cultural influences on the use of menthol cigarettes among Blacks and Hispanics. *Nicotine Tobacco Research.* 2004;6 Suppl 1:S29-41.

23. Nollen NL, Cox LS, Yu Q, et al. A clinical trial to examine disparities in quitting between African-American and White adult smokers: Design, accrual, and baseline characteristics. *Contemporary clinical trials.* 2016;47:12-21. PMCID:PMC481877.

24. Allen B, Jr., Unger JB. Sociocultural correlates of menthol cigarette smoking among adult African Americans in Los Angeles. *Nicotine Tobacco Research.* 2007;9(4):447-451.

25. Patterson F, Benowitz N, Shields P, et al. Individual differences in nicotine intake per cigarette. *Cancer Epidemiology, Biomarkers & Prevention.* 2003;12(5):468-471.

26. Ho MK, Mwenifumbo JC, Al Koudsi N, et al. Association of nicotine metabolite ratio and CYP2A6 genotype with smoking cessation treatment in African-American light smokers. *Clinical Pharmacology & Therapeutics.* 2009;85(6):635-643.

27. Ho MK, Faseru B, Choi WS, et al. Utility and relationships of biomarkers of smoking in African-American light smokers. *Cancer Epidemiology, Biomarkers & Prevention.* 2009;18(12):3426-3434.

28. Benowitz NL, Bernert JT, Caraballo RS, Holiday DB, Wang J. Optimal serum cotinine levels for distinguishing cigarette smokers and nonsmokers within different racial/ethnic groups in the United States between 1999 and 2004. *American Journal of Epidemiology* 2009;169(2):236-248.

29. Fu S, Kodl M, Joseph A, et al. Racial/ethnic disparities in the use of nicotine replacement therapy and quit ratios in lifetime smokers ages 25 to 44 years. *Cancer Epidemiology, Biomarkers & Prevention.* 2008;17(7):1640-1647.

30. Fagan P, Moolchan ET, Lawrence D, Fernander A, Ponder PK. Identifying health disparities across the tobacco continuum. *Addiction (Abingdon, England).* 2007;102 Suppl 2:5-29.

31. Soulakova JN, Crockett LJ. Level of Cigarette Consumption and Duration of Smoking Abstinence During Failed Quit Attempts Among Long-Term Daily Smokers: the Role of Race/Ethnicity and Cessation Aids. *J Racial Ethn Health Disparities.* 2017.

32. Soulakova JN, Li J, Crockett LJ. Race/ethnicity and intention to quit cigarette smoking. *Preventive medicine reports.* 2017;5:160-165.

33. Cox LS, Okuyemi K, Choi WS, Ahluwalia JS. A review of tobacco use treatments in U.S. ethnic minority populations. *American Journal of Health Promotion.* 2011. PMCID:PMC4494679.

34. Benowitz N. Smoking cessation trials targeted to racial and economic minority groups. *JAMA*. 2002;288(4):497-499.

35. Burchard EG, Borrell LN, Choudhry S. Latino populations: A unique opportunity for the study of race, genetics, and social environment in epidemiological research. *American Journal of Public Health.* 2005;95(12):2161-2168.

36. Webb MS. Treating tobacco dependence among African Americans: a meta-analytic review. *Health Psychol.* 2008;27(3S):S271-282.

37. Lawrence D, Graber JE, Mills SL, Meissner HI, Warnecke R. Smoking cessation interventions in U.S. racial/ethnic minority populations: an assessment of the literature. *Preventive medicine.* 2003;36(2):204-216.

38. Robles GI, Singh-Franco D, Ghin HL. A review of the efficacy of smoking-cessation pharmacotherapies in nonwhite populations. *Clin Ther.* 2008;30(5):800-812.

39. Ahluwalia JS, McNagny SE, Clark WS. Smoking cessation among inner-city African Americans using the nicotine transdermal patch. *J Gen Intern Med.* 1998;13(1):1-8.

40. Ahluwalia JS, Harris KJ, Catley D, Okuyemi KS, Mayo MS. Sustained-release bupropion for smoking cessation in African Americans: A randomized controlled trial. *Jama.* 2002;288(4):468-474.

41. Cox LS, Nollen NL, Mayo MS, et al. Bupropion for smoking cessation in African American light smokers: a randomized controlled trial. *Journal of the National Cancer Institute.* 2012;104(4):290-298. PMCID:PMC3283533.

42. Cox LS, Nollen, N., Mayo, M., Faseru, B., Ellerbeck, E., Snow, T., Liebmann, E., Tyndale, R., Benowitz, N., Ahluwalia, J. S. Increasing abstinence in African American daily smokers: Results from a randomized, placebo-controlled clinical trial of varenicline. . Annual Meeting of the European Chapter of the Society for Research on Nicotine and Dependence; September 2019, 2019; Oslo, Norway.

43. Murray RP, Connett JE, Buist AS, Gerald LB, Eichenhorn MS. Experience of Black participants in the Lung Health Study smoking cessation intervention program. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2001;3(4):375-382.

44. Gariti P, Lynch K, Alterman A, Kampman K, Xie H, Varillo K. Comparing smoking treatment programs for lighter smokers with and without a history of heavier smoking. *Journal of Substance Abuse Treatment.* 2009;37(3):247-255.

45. Andrews JO, Felton G, Ellen Wewers M, Waller J, Tingen M. The effect of a multi-component smoking cessation intervention in African American women residing in public housing. *Res Nurs Health.* 2007;30(1):45-60.

46. Webb MS, de Ybarra DR, Baker EA, Reis IM, Carey MP. Cognitive-behavioral therapy to promote smoking cessation among African American smokers: A randomized clinical trial. *Journal of Consulting & Clinical Psychology.* 2010;78:24-33.

47. Shiffman S. Nicotine lozenge efficacy in light smokers. *Drug and Alcohol Dependence.* 2005;77(3):311-314.

48. Ebbert JO, Croghan IT, Hurt RT, Schroeder DR, Hays JT. Varenicline for Smoking Cessation in Light Smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2016;18(10):2031-2035.

49. Ahluwalia JS, Okuyemi K, Nollen N, et al. The effects of nicotine gum and counseling among African American light smokers: A 2 x 2 factorial design. *Addiction (Abingdon, England).* 2006;101(6):883-891.

50. Nollen NL, Cox LS, Mayo MS, Ellerbeck EF, Madhusudhana S, Ahluwalia JS. A randomized clinical trial of counseling and nicotine replacement therapy for treatment of African American non-daily smokers: Design, accrual, and baseline characteristics. *Contemporary clinical trials.* 2018;70:72-82. PMID:30657926.

51. Cropsey KL, Weaver MF, Eldridge GD, Villalobos GC, Best AM, Stitzer ML. Differential success rates in racial groups: results of a clinical trial of smoking cessation among female prisoners. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2009;11(6):690-697.

52. Croghan IT, Hurt RD, Ebbert JO, et al. Racial differences in smoking abstinence rates in a multicenter, randomized, open-label trial in the United States. *Z Gesundh Wiss.* 2010;18(1):59-68.

53. Nollen N, Mayo MS, Cox LS, et al. Differences in varenicline efficacy for smoking cessation among black and white smokers. Manuscript submitted for publication.

54. Nollen NL, Cox, L. S., Mayo, M. S., Ellerbeck, E. F., Ahluwalia, J. S. Counseling and nicotine replacement therapy for treatment of black-non-daily smokers: A randomized trial. *Manuscript submitted for publication.* 2019.

55. Nollen NL, Cox LS, Nazir N, et al. A pilot clinical trial of varenicline for smoking cessation in black smokers. *Nicotine & Tobacco Research.* 2011. PMCID:PMC3203399.

56. Hays JT, Leischow SJ, Lawrence D, Lee TC. Adherence to treatment for tobacco dependence: Association with smoking abstinence and predictors of adherence. *Nicotine & Tobacco Research.* 2010;12(6):574-581.

57. Shiffman S, Sweeney CT, Ferguson SG, Sembower MA, Gitchell JG. Relationship between adherence to daily nicotine patch use and treatment efficacy: Secondary analysis of a 10 week randomized, double-blind, placebo-controlled clinical trial simulating over-the-counter use in adult smokers. *Clinical Therapeutics.* 2008;30(10):1852-1858.

58. Cokkinides VE, Halpern MT, Barbeau EM, Ward E, Thun MJ. Racial and ethnic disparities in smoking-cessation interventions: Analysis of the 2005 National Health Interview Survey. *American Journal of Preventive Medicine.* 2008;34(5):404-412.

59. Hollands GJ, McDermott MS, Lindson-Hawley N, Vogt F, Farley A, Aveyard P. Interventions to increase adherence to medications for tobacco dependence. *The Cochrane database of systematic reviews.* 2015(2):CD009164.

60. Catz SL, Jack LM, McClure JB, et al. Adherence to varenicline in the COMPASS smoking cessation intervention trial. *Nicotine & Tobacco Research.* 2011;13(5):361-368.

61. Nollen NL, Mayo MS, Ahluwalia JS, et al. Factors associated with discontinuation of bupropion and counseling among African American light smokers in a randomized clinical trial. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine.* 2013;46(3):336-348.

62. Hollands G, McDermott M, Lindson-Hawley N, Vogt F, Farley A, Aveyard P. Interventions to increase adherence to medications for tobacco dependence. *Cochrane Database of Systematic Reviews.* 2015(2).

63. Mooney ME, Sayre SL, Hokanson PS, Stotts AL, Schmitz JM. Adding MEMS feedback to behavioral smoking cessation therapy increases compliance with bupropion: A replication and extension study. *Addictive behaviors.* 2007;32(4):875-880.

64. Benowitz NL. Chronic disease management approach to treating tobacco addiction: comment on "Nicotine therapy sampling to induce quit attempts among smokers unmotivated to quit". *Arch Intern Med.* 2011;171(21):1907-1909.

65. Ellerbeck EF, Mahnken JD, Cupertino AP, et al. Effect of varying levels of disease management on smoking cessation. *Annals of Internal Medicine.* 2009;150(7):437-446.

66. Bouton ME. Why behavior change is difficult to sustain. *Preventive medicine.* 2014;68:29-36.

67. Kirshenbaum AP, Olsen DM, Bickel WK. A quantitative review of the ubiquitous relapse curve. *J Subst Abuse Treat.* 2009;36(1):8-17.

68. Hall SM, Humfleet GL, Munoz RF, Reus VI, Robbins JA, Prochaska JJ. Extended treatment of older cigarette smokers. *Addiction (Abingdon, England).* 2009;104(6):1043-1052.

69. Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, Hajek P. Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev.* 2019;2:CD003999.

70. Schnoll R, Leone F, Veluz-Wilkins A, et al. A randomized controlled trial of 24 weeks of varenicline for tobacco use among cancer patients: Efficacy, safety, and adherence. *Psychooncology.* 2019;28(3):561-569.

71. Schnoll RA, Patterson F, Wileyto EP, et al. Efficacy of Extended Duration Transdermal Nicotine Therapy: A Randomized Trial. *Annals of internal medicine.* 2010;152(3):144-151.

72. Schnoll RA, Goelz PM, Veluz-Wilkins A, et al. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA internal medicine.* 2015;175(4):504-511.

73. Laude JR, Bailey SR, Crew E, et al. Extended treatment for cigarette smoking cessation: a randomized control trial. *Addiction (Abingdon, England).* 2017;112(8):1451-1459.

74. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *The Cochrane database of systematic reviews.* 2013(5):Cd009329.

75. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews.* 2007(1).

76. Cox L, Faseru B, Mayo M, et al. Design, baseline characteristics, and retention of African American light smokers into a randomized trial involving biological data. *Trials.* 2011;12(1):22. PMCID:PMC3038942.

77. McNeill A, Leonardi-Bee J, Myers K, McRobbie H. Smoking relapse: Patterns, prevention, and future perspectives. Society for Research on Nicotine and Tobacco - Europe; 2010; Bath, UK.

78. Hays JT, Hurt RD, Rigotti NA, et al. Sustained release buproprion for pharmacologic relapse prevention after smoking cessation. *Annals of Internal Medicine.* 2001;135:423-433.

79. Croghan IT, Hurt RD, Dakhil SR, et al. Randomized comparison of nicotine inhaler and bupropion for smoking cessation and relapse prevention. *Mayo Clinic Proceedings.* 2007;82(2):186-195.

80. Covey LS, Glassman AH, Jiang H, et al. A randomized trial of bupropion and/or nicotine gum as maintenance treatment for preventing smoking relapse. *Addiction (Abingdon, England).* 2007;102(8):1292-1302.

81. Killen JD, Fortmann SP, Murphy GM, et al. Extended treatment with bupropion SR for cigarette smoking cessation *Journal of Consulting and Clinical Psychology.* 2006;74(2):286-294.

82. Hays JT, Hurt RD, Decker PA, Croghan IT, Offord KP, Patten CA. A randomized, controlled trial of bupropion sustained-release for preventing tobacco relapse in recovering alcoholics. *Nicotine & Tobacco Research.* 2009;11(7):859-867.

83. Hurt RD, Krook JE, Croghan IT, et al. Nicotine patch therapy based on smoking rate followed by bupropion for prevention of relapse to smoking. *J Clin Oncol.* 2003;21(5):914-920.

84. Agboola S, McNeill A, Coleman T, Leonardi Bee J. A systematic review of the effectiveness of smoking relapse prevention interventions for abstinent smokers. *Addiction (Abingdon, England).* 2010;105(8):1362-1380.

85. Taylor M, Leonardi-Bee J, Agboola S, McNeill A, Coleman T. Cost effectiveness of interventions to reduce relapse to smoking following smoking cessation. *Addiction (Abingdon, England).* 2011.

86. Gonzales D, Jorenby DE, Brandon TH, Arteaga C, Lee TC. Immediate versus delayed quitting and rates of relapse among smokers treated successfully with varenicline, bupropion SR or placebo. *Addiction (Abingdon, England).* 2010;105(11):2002-2013.

87. Hajek P, Stead LF, West R, Jarvis M, Hartmann-Boyce J, Lancaster T. Relapse prevention interventions for smoking cessation. *The Cochrane database of systematic reviews.* 2013(8):Cd003999.

88. Pacek LR, McClernon FJ, Bosworth HB. Adherence to pharmacological smoking cessation interventions: A literature review and synthesis of correlates and barriers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2017.

89. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews.* 2014(1).

90. Piper ME, Federmen EB, McCarthy DE, et al. Using mediational models to explore the nature of tobacco motivation and tobacco treatment effects. *J Abnorm Psychol.* 2008;117(1):94-105.

91. McCarthy DE, Piasecki TM, Lawrence DL, Jorenby DE, Shiffman S, Baker TB. Psychological mediators of bupropion sustained-release treatment for smoking cessation. *Addiction (Abingdon, England).* 2008;103(9):1521-1533.

92. Garten S, Falkner RV. Role of mentholated cigarettes in increased nicotine dependence and greater risk of tobacco-attributable disease. *Preventive medicine.* 2004;38(6):793-798.

93. Ahijevych K, Garrett BE. Menthol pharmacology and its potential impact on cigarette smoking behavior. *Nicotine & Tobacco Research.* 2004;6(Suppl 1):S17-S28.

94. Benowitz NL, Perez-Stable EJ, Fong I, Modin G, Herrera B, Jacob P. Ethnic differences in N-Glucuronidation of nicotine and cotinine. *Journal of Pharmacology and Experimental Therapeutics.* 1999;291(3):1196-1203.

95. Faseru B, Nollen NL, Mayo MS, et al. Predictors of cessation in African American light smokers enrolled in a bupropion clinical trial. *Addictive behaviors.* 2013;38(3):1796-1803.

96. Nollen NL, Mayo MS, Cox LS, et al. Predictors of quitting among African American light smokers enrolled in a randomized, placebo-controlled trial. *Journal of General Internal Medicine.* 2006;21(6):590-595. PMCID:PMC1924642.

97. Benowitz NL, Dains KM, Dempsey D, Yu L, Jacob P. Estimation of nicotine dose after low-level exposure using plasma and urine nicotine metabolites. *Cancer Epidemiology, Biomarkers & Prevention.* 2010;19(5):1160-1166.

98. Dempsey D, Tutka P, Jacob P, 3rd, et al. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. *Clinical pharmacology and therapeutics.* 2004;76(1):64-72.

99. Patterson F, Schnoll RA, Wileyto EP, et al. Toward personalized therapy for smoking cessation: a randomized placebo-controlled trial of bupropion. *Clinical pharmacology and therapeutics.* 2008;84(3):320-325.

100. Lerman C, Jepson C, Wileyto EP, et al. Genetic variation in nicotine metabolism predicts the efficacy of extended-duration transdermal nicotine therapy. *Clinical pharmacology and therapeutics.* 2010;87(5):553-557.

101. Zhu AZ, Cox LS, Nollen N, et al. CYP2B6 and bupropion's smoking-cessation pharmacology: the role of hydroxybupropion. *Clinical pharmacology and therapeutics.* 2012;92(6):771-777. PMCID: PMC3729209.

102. Smith PH, Weinberger AH, Zhang J, Emme E, Mazure CM, McKee SA. Sex Differences in Smoking Cessation Pharmacotherapy Comparative Efficacy: A Network Meta-analysis. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2017;19(3):273-281.

103. Hays JT, Hurt RD, Rigotti NA, et al. Sustained release bupropion for pharmacologic relapse prevention after smoking cessation. *Ann Intern Med.* 2001;135:423-433.

104. Nollen NL, Mayo MS, Cox LS, et al. Factors that Explain Differences in Abstinence between Black and White Smokers: A Prospective Intervention Study. *Journal of the National Cancer Institute.* 2019.

105. Cox LS, Cupertino AP, Mussulman LM, et al. Design and baseline characteristics from the KAN-QUIT disease management intervention for rural smokers in primary care. *Preventive medicine.* 2008;47(2):200-205. PMCID:PMC2577567.

106. Okuyemi K, Cox LS, Nollen N, et al. Baseline design and data from KIS II: A randomized clinical trial of African American light smokers. *Am J Health Promotion.* 2007. PMID:17233236.

107. Perkins KA, Conklin, C. A., Levine, M. D. *Cognitive-behavioral therapy for smoking cessation: A practical guidebook to the most effective treatments.* New York: Routledge; 2008.

108. Webb Hooper M, Antoni MH, Okuyemi K, Dietz NA, Resnicow K. Randomized Controlled Trial of Group-Based Culturally Specific Cognitive Behavioral Therapy Among African American Smokers. *Nicotine & Tobacco Research.* 2017;19(3):333-341.

109. Harris KJ, Ahluwalia, J. S., Okuyemi, K. S., Turner, J. R., Woods, M. N., Backinger, C., Resnicow, K. Addressing cultural sensitivity in a smoking cessation intervention: Development of the Kick It at Swope project. . *Journal of Community Psychology.* 2001;29(4):447-458.

110. Catley D, Goggin K, Harris KJ, et al. A Randomized Trial of Motivational Interviewing: Cessation Induction Among Smokers With Low Desire to Quit. *American journal of preventive medicine.* 2016;50(5):573-583.

111. Swan GE, McAfee T, Curry SJ, et al. Effectiveness of bupropion sustained release for smoking cessation in a health care setting: A randomized trial. *Archives of Internal Medicine.* 2003;163(19):2337-2344.

112. SRNT. Biochemical verification of tobacco use and cessation. *Nicotine & Tobacco Research.* 2003;5(1):13-25.

113. Jacob P, 3rd, Hatsukami D, Severson H, Hall S, Yu L, Benowitz NL. Anabasine and anatabine as biomarkers for tobacco use during nicotine replacement therapy. *Cancer Epidemiol Biomarkers Prev.* 2002;11(12):1668-1673.

114. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: Issues and recommendations. *Nicotine Tobacco Research.* 2003;5(1):13-25.

115. Goniewicz ML, Eisner MD, Lazcano-Ponce E, et al. Comparison of urine cotinine and the tobacco-specific nitrosamine metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and their ratio to discriminate active from passive smoking. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2011;13(3):202-208.

116. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction.* 1991;86(9):1119-1127.

117. Smith SS, Piper ME, Bolt DM, et al. Development of the Brief Wisconsin Inventory of Smoking Dependence Motives. *Nicotine & Tobacco Research.* 2010;12(5):489-499.

118. Brown RA, Burgess ES, Sales SD, Whiteley JA, Evans DM, Miller IW. Reliability and validity of a smoking timeline follow-back interview. *Psychology of Addictive Behaviors.* 1998;12(2):101-112.

119. Cox LS, Mayo MS, Krebill R, et al. Assessment of daily smoking using timeline follow-back (TLFB) among African American smokers. Society for Research on Nicotine and Tobacco (SRNT); 2010; Baltimore, MD.

120. Baker T, Mermelstein R, Collins L, et al. New methods for tobacco dependence treatment research. *Annals of Behavioral Medicine.* 2011;41(2):192-207.

121. Sheldon C, Kamarck T, Mermelstein R. A global measure of perceived stress. *Journal of Health and Social Behavior.* 1983;24(4):385-396.

122. Krieger N, Smith K, Naishadham D, Hartman C, Barbeau EM. Experiences of discrimination: Validity and reliability of a self-report measure for population health research on racism and health. *Social Science & Medicine.* 2005;61(7):1576-1596.

123. Thomas SB, Quinn SC, Butler J, Fryer CS, Garza MA. Toward a fourth generation of disparities research to achieve health equity. *Annual Review of Public Health.* 2011;32:399-416.

124. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry.* 1986;43:289-294.

125. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2001;3(1):7-16. PMID:11260806.

126. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology.* 1988;54(6):1063-1070.

127. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement.* 1977;1(3):385-401.

128. Buchanan TS, Berg CJ, Cox LS, et al. Adherence to varenicline among African American smokers: an exploratory analysis comparing plasma concentration, pill count, and self-report. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2012;14(9):1083-1091. PMCID:PMC3432278.

129. Kalichman SC, Amaral CM, Cherry C, et al. Monitoring medication adherence by unannounced pill counts conducted by telephone: Reliability and criterion-related validity. *HIV Clinical Trials.* 2008;9(5):298-308.

130. Kalichman SC, Amaral CM, Stearns H, et al. Adherence to antiretroviral therapy assessed by unannounced pill counts conducted by telephone. *JGIM: Journal of General Internal Medicine.* 2007;22(7):1003-1006.